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The Use of the Rice Diet in the Treatment of Hypertension in Nonhospitalized Patients: This report covers the first six months of a study of a group of nonhospitalized patients with hypertension who were treated with the rice diet. As far as possible, nothing was changed in the daily routine of the patients except the diet. If they were ambulatory and working, they continued these activities; if they were inactive because of their illness, they remained inactive until improvement, if it did occur, warranted a more strenuous life.

Of 68 patients originally started on the rice diet, 4 had hypertension with renal failure; 3 had cardiac failure with edema; 5 had coronary-artery disease with severe angina pectoris and no hypertension; one had severe coronary-artery disease with hypertension; and 55 had essential hypertension.

This report mainly concerns the 55 patients with essential hypertension. Of these, 18 were excluded from the study because of non-cooperation. Some failed to return for subsequent visits after having been advised to follow the diet. Others, after a few days, expressed unwillingness to remain on the diet, and still others, who did not admit their dietary divergence, were excluded because their 24-hour urinary chloride excretions (expressed as sodium chloride) were so high that it was obvious that they were not adhering to the regimen. Also, because coronary occlusion developed in 3 patients within the first few days or weeks after they had been started on the diet, they were excluded.

The 34 patients who cooperated and were considered satisfactory for study had had well established, known hypertension for at least three or more years. Many of them had been under the observation of Doctor Contratto, one of the authors, during this time; others had been under the care of other physicians. Of this number, 21 were women and 13 were men. They varied in age from 35 to 69 years.

Before being started on the diet, each patient had a physical examination that included an electrocardiogram, blood counts, urinalysis, and determinations of 24-hour urinary chloride excretion, blood cholesterol, blood urea nitrogen, total protein, albumin-globulin ratio, and blood chloride. Each patient received a copy of the rice diet, as devised by Kempner, which contains in 2000 calories not more than 5 Gm. of fat and about 20 Gm. of protein derived from rice and fruit, and not more than 200 mg. of chloride and 150 mg. of sodium:

> A patient takes an average of from 250 to 350 Gm. of rice (dry weight) daily; any kind of rice may be used provided no sodium, chloride, milk, etc. has been added during its processing. . . All fruit juices and fruits are allowed, with the exception of nuts, dates, avocados and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. . . Usually no water is given and the fluid intake is limited to from 700 to 1,000 c.c. of fruit juice per day.

Breakfast consists of 2 or 3 ounces of rice (uncooked weight) with sugar or honey, two thirds of a glass of prune juice, a baked apple and a baked grapefruit. At 10 a.m., half a glass of orange juice is included, with grapes and an orange. Lunch consists of rice (as at breakfast) with sugar or honey, five eighths of a glass of orange juice, one split banana with six slices of apple, a good many raisins, and a baked slice of fresh pineapple with a cherry in the center. At 3 p. m. half a glass of orange juice, dried soft peaches and an apple are taken. Supper consists of the rice with sugar or honey, two thirds of a glass of orange juice and a fruit plate (apricot, four sections of grapefruit, four orange sections, and four figs). At 9 p. m. half a glass of orange juice is taken.

Supplementary multiple vitamins were added, usually 2 unicaps per day, and iron when the patient was menstruating. Modified diets were outlined, mimeographed, and ready for the patients' use as soon as indicated by their condition. Directions for collecting the 24-hour specimen of urine were also printed. It was believed that it was necessary to see these patients at least every two weeks at first to collect the specimen for urinary chloride determinations, as advised by Kempner; to check on the diet and vary it in most cases; and to determine the blood pressure. Patients who were too ill at the time, who for some other reason were unable to report for a regular 2-week checkup, or who, because of psychologic reasons, were having difficulty following the regimen were seen by a volunteer worker, one of the authors, at regular intervals in their homes. She answered any question about the use and preparation of the diet, collected the urine and blood specimens, recorded the blood pressure and pulse, and took an electrocardiogram when it was considered necessary. One of her important duties on these visits was to reassure the patients, making it understood that in most cases the diet was effective, that it was not necessarily a permanent one, and that although they might have periods of extreme weakness and fatigue, and even depression, they would soon feel better. This plan worked well, and it is believed that many patients who would otherwise not have adhered to the diet followed the regimen faithfully and even cheerfully.

All sedation and medication were withdrawn from these patients as soon as possible, especially from those who were taking sodium pentobarbital or phenobarbital. The patients were expected to remain rigidly on the strict rice diet for a period of three months unless a satisfactory drop in blood pressure occurred before that time. With some patients, however, because of their age, or for psychologic reasons, it was necessary to modify the diet before the 3-month period had elapsed. Patients who, during this period, had remained strictly on the diet and who also had satisfactory urinary chloride excretions but whose blood pressure did not show significant drop were considered "failures," and the dietary regimen was concluded.

The diet was gradually modified for patients whose blood-pressure readings dropped satisfactorily. The first modification was the addition of one egg

once a week, half a cup of nonleguminous vegetables (carrots, broccoli, celery, cabbage, asparagus, beets, spinach and so forth), boiled without salt, once a day and, if desired, a cup of coffee or tea once a day, with sugar, but without milk or cream; no salt or fat was included in any of the modifications, all of which contained the amounts of rice specified previously. The patient stayed on this regimen for from two weeks to a month. If the blood-pressure readings were satisfactory at the end of this time, 4 ounces of lean meat, fish, liver, or chicken three times weekly was added to the diet, the egg being taken three times a week and the nonleguminous vegetable once a day. The meat or fish was boiled or broiled, without salt or salt-containing substances. At this time, some patients were allowed salt-free bread, two slices daily. If progress was satisfactory after another month, the diet was again modified to allow 4 ounces of meat and so forth, as mentioned above, at one meal daily, half a cup each of two nonleguminous vegetables, one egg, either boiled or poached, three times weekly, and a baked or boiled white or sweet potato twice weekly. The fourth modification of the diet was advised only for those patients whose blood-pressure readings had remained satisfactory after having been on the third modification for a month. This addition consisted of one egg daily if desired, meat and so forth once daily, any of the nonleguminous vegetables as desired, and a baked or boiled potato each day.

The blood-pressure readings were always taken in the same manner. Three readings were taken at intervals of five or ten minutes with the patient in the recumbent position. A mercury sphygmomanometer was always used, and the readings taken from the right arm. An average of the three readings was considered the actual reading for that visit. Determinations of the blood urea nitrogen, blood chloride, total protein, albumin-globulin ratio and blood cholesterol were done at monthly intervals.

All the patients lost weight during the first and second months. The amount of weight loss depended upon the weight initially, but a loss of from 10 to 15 pounds during this period was not unusual. The average weight of the patients was 155 pounds at the beginning, 146 pounds six weeks later, and 144 pounds after three months - an average loss of 11 pounds per patient. Although after six months the average weight of the group was only 139 pounds, this did not mean that the patients were continuing to lose weight during the entire period, but rather that the failures had been excluded after three months. None of these patients were obese. In this series, the obese patients failed to cooperate.

The urinary chloride determinations averaged 8.6 Gm. before the diet was started. These dropped rapidly, going below 1 Gm. within the first two weeks and less than 0.5 Gm. within the first 6-week period, and in some patients as low as 0.1 Gm. As the diet was modified, the urinary chloride began to rise, reaching an average of 1.10 Gm. shortly after the 3-month period, and 1.31 Gm. at the end of the 6-month period.

The blood-pressure readings in the patients with essential hypertension averaged 210 systolic, 120 diastolic, before the regimen was started, the highest being 260 systolic, 160 diastolic; the lowest, 190 systolic, 102 diastolic. At three months, the average was 158 systolic, 100 diastolic.

The systolic blood pressure dropped to 150 or below and the diastolic to 100 or below in 16 patients (10 women and 6 men). The blood pressure dropped 50 or more systolic and 20 or more diastolic in 8 patients (2 men and 6 women). Twenty-four patients, or 70 percent, showed a definite and persistent drop in blood pressure, and 10, or 30 percent, did not.

The lowest readings were observed between the sixth week and the third month of treatment, while the patient was on the strict rice diet. As the diet was modified, a slight elevation of the blood pressure was observed, but in none of the successful cases did the pressure return to its original level.

The blood chemistry studies were made in each case every month for the first three months. None of the patients showed any change, with the exception of a decrease in the average cholesterol concentration in some cases. In none of the patients observed did a sodium or a chloride deficiency develop. During the hot summer months, these patients suffered no more from the heat than persons on normal diets. Several patients considered that they had a better summer than they had had in years.

All the patients experienced a period of weakness, which generally occurred from about the tenth to the twenty-first day and in some cases was even accompanied by a psychologic depression that required much understanding on the part of the physician and the volunteer worker. This period was only temporary, however, lasting at the most two or three weeks; after this time, although no change was made in the diet, the patients began to feel stronger and better than they had felt before the diet. They became free of headaches, which had been the predominating complaint; they felt much less tension and nervousness; and they were finally able to relax, rest, and sleep well without sedation.

Two of the authors' five representative case histories follow:

A. P., a 65-year-old woman, was first seen in June, 1943, when her blood pressure was 210/110, with a history of known hypertension for 10 years before this visit. Her main complaint was a "pressure band" across the back of her head, which she stated had been present for approximately 15 years. A period of rest and small doses of phenobarbital were advised. At yearly examinations, her blood-pressure readings varied between 198/118 and 230/130. In June, 1947, her blood pressure was 230/130; she was started on the rice diet. After 2 weeks, her blood pressure was 180/110. After 6 weeks on the diet, her blood pressure had decreased to 150/90, and she felt much improved. She no longer complained of the pressure sensation in her head. Upon her next

examination (16 August 1947), her blood pressure was 130/90, and she was placed on a modified diet, which included meat, fish, vegetables, and salt-free bread. The patient looked and felt markedly improved, and was capable of much more physical exertion than she had been for years. On 16 September 1947, her blood pressure was 150/100. These figures have been maintained, and although her diet has been modified to allow meat, vegetables, and salt-free bread each day, the urinary chloride excretion has remained below 0.7 Gm.

F. G., a 69-year-old man, when first seen had a blood pressure of 220/110 and a urinary chloride excretion of 11.65 Gm. During the previous 6 months, he had experienced precordial pain and breathlessness on exertion. Kidney-function tests were negative. Although the patient was not working, he was ambulatory, and no other change in his routine was prescribed with the exception of the rice diet. Ten days later, his blood pressure had decreased to 174/92, and the urinary chloride excretion to 0.79 Gm. On 18 November 1947, his blood pressure was 128/80, the urinary chloride excretion was 0.20 Gm., and the patient had lost 14 pounds. The diet was modified at this time, and on 30 December, his blood pressure was 148/85, and the urinary chloride excretion was 2.08 Gm. On 24 February 1948, the blood pressure was 150/84, and the urinary chloride excretion was 4.77 Gm. On 7 April 1948, when the patient was last seen, the blood pressure was 176/92, and the urinary chloride excretion was 4.31 Gm. Although this patient admitted some slight deviations from his diet, which might very well account for the increase in the urinary chloride excretion, it was decided to allow him to continue on the modified regimen because he was feeling so much better and had returned to work.

The rice diet has been found to be a practical, inexpensive, and simple method for reducing blood pressure. It requires, however, understanding and cooperation on the part of the patient to maintain it strictly because it is a rigid departure from what is usually considered a "normal" diet.

In most cases, the loss of weight was welcomed and, at a certain point in the course of treatment, became stabilized. Patients who were underweight initially lost less than those who were overweight, but this condition likewise became adjusted as the routine progressed. In Doctor Contratto's opinion, loss of weight has little or nothing to do with a drop in blood pressure, for several of the patients who were overweight had formerly been placed on low-calorie diets, and their blood pressure had not been measurably altered. On the subject of weight loss, Kempner states:

> It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements; in such cases, the amount of food must be increased, unless reduction of weight is indicated. Another reason may be that the patient does not eat the full

amount of his diet during the first period of adjustment. The most frequent cause is the loss of visible edema; one patient with marked edema, for example, lost 63 lbs. within the first sixteen days on the diet.

Too much emphasis cannot be placed on the necessity for obtaining the urinary chloride determinations at two-week intervals. Aside from the value to the physician, scientifically, it is a valuable aid psychologically in maintaining the patient on the strict rice diet. Since it is obviously natural for patients to desire other food than that prescribed, it is carefully explained that any deviation from the strict diet will be easily observed in these tests. This advice, in Doctor Contratto's experience, has proved an inhibitory factor in some patients whose need and desire for a varied menu was greater than that in others.

It was found difficult, if not impossible, to have a patient revert to the strict rice diet if the results on the modified diet had proved to be unsatisfactory. In the future, it will be necessary to maintain certain patients for a longer period on the strict rice diet. Also, the modified diets have been considerably altered to eliminate eggs, liver, and certain nonleguminous vegetables high in sodium content - notably, spinach, beets, and kale. The new modified diets add considerably less in quantity at each modification, and there are six diets instead of four. The results of these changes will be discussed in a subsequent publication.

Although these observations cover a limited period, it is Doctor Contratto's belief that the rice diet for hypertension offers the greatest hope so far for the medical treatment in a disease, in which, to date, the therapeutic results have been notoriously poor.

The mechanism through which the reduction of blood pressure is achieved is not known, but it is difficult to escape the notion that the sodium ion plays a role in a manner not yet clear. (New England J. Med., 7 Oct. '48 - A. W. Contratto and M. B. Rogers)

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Etiology of Acute Pancreatitis: Acute pancreatitis is characterized by the dramatic onset of abdominal pain, nausea, vomiting, and collapse, even to the state of shock. In rare cases, abdominal trauma, rupture of an aneurysm, or infections are responsible, but in the large majority the cause is not definitely established.

The pathology of acute pancreatitis varies considerably. Although some workers have regarded the degrees of involvement as different disease entities, it is probable that they are stages of the same process. In the cases in which opportunity for autopsy develops, the inflammatory process is usually patchy.

Some parts of the gland show destruction of the lobules, others show necrosis of a few acini around the periphery of the lobules, and still others show normal lobules with inflammatory cells in the interlobular septa. Fat necrosis is irregular in its distribution. When the walls of blood vessels are involved, hemorrhagic areas are found intermingled with the areas of fat necrosis and parenchymal destruction. At a later stage, degrees of inflammation ranging from a few leucocytes to abscess formation are found.

The authors produced acute pancreatic inflammation and fat necrosis in a high percentage of starving animals by tying the pancreatic ducts and stimulating the pancreas by feeding, acetylcholine and eserine, pilocarpine, stimulation of the vagus, and secretin. The most extensive and consistent damage resulted when the animals were fed two hours before ligation of the pancreatic ducts so that this took place at the height of digestion. Four stages of inflammation were noted.

The question arises whether such changes experimentally produced are necessarily the same as those of acute pancreatitis in human beings. The patchy distribution of severe lesions is quite characteristic of acute pancreatitis and the finding of normal lobules alongside those that are badly damaged is a common one. Eggers reported a very interesting fatal case of acute pancreatitis in which there were many normal areas of gland tissue. The necrosis and inflammation had proceeded along the interlobular septa and had attacked the periphery of the lobules first. This same picture was found in the authors' experiments. In reconstructing the sequence of events on the basis of the four degrees of pancreatic involvement noted in the experimental animals, something of this order occurs. The pancreas is secreting actively, and suddenly the outlets are obstructed. The pancreatic juice ruptures the ducts which run along the interlobular septa and initiate an inflammatory reaction as the result of tissue damage. If the secretory pressure and enzymatic concentration are not great, the process may end at this stage, but if the secretory pressure is high or the enzymatic content of the juice is high, the autodigestion of tissue proceeds to an attack of the acini on the periphery of the lobules as well as a penetration into the lobules. The patchy distribution of severe lesions can readily be explained by the location of the ductal rupture. Certainly the ducts will not rupture throughout their entire length, but rather in a few places. Wherever they rupture, the pancreatic juices will escape and produce local damage of an intensity commensurate with the volume and enzyme content of the extruded secretion.

Based upon the authors' concepts, most of the experimental and clinical facts can be rationalized. The occurrence of acute pancreatitis after a heavy meal at the height of digestion has been noted by clinicians for years. This is the time when the pancreatic juice contains the greatest concentration of enzymes. An obstruction of the gland at this time will thus cause the greatest autodigestion and tissue damage.

Several causes for the obstruction to the pancreatic ducts in the human being have been noted. Mechanical factors such as stones and round worms at the ampulla have been reported by Ravdin and Johnston. Archibald argued that in the absence of such elements, edema and spasm of the sphincter of Oddi could produce obstruction. He observed this spasm in cats. With the pressure in the biliary tree kept constant by a manometer, the fluid was seen to enter the duodenum at intervals rather than as a constant flow. In the light of clinical studies with tubes in the common duct, this seems quite reasonable. Best and Hicken found marked elevation in the intraductal pressure after cholecystectomy, and they found that spasm of the sphincter caused complete although temporary obstruction. McGowan, Butsch, and Walters reported a marked increase in bile pressure along the common duct after morphine sulfate had been given, indicating mechanical blockage by spasm. This was relieved by glyceryl trinitrate. Ivy and Sandbloom showed that blockage of the biliary passages by spasm is possible in normal human subjects and that magnesium sulfate placed in the duodenum relieves the stoppage in a few minutes. Any blockage of the bile passages at the ampulla will also obstruct pancreatic secretion. That spasm of the smooth muscle about the ducts may be causative in acute pancreatitis is suggested by Elman, who noted that glyceryl trinitrate placed under the tongue shortly after an acute attack of pancreatitis has begun may lead to a dramatic abortion of the attack.

This relief by glyceryl trinitrate may not be due entirely to relief of spasm in the sphincter of Oddi. It may also relieve spasm of the pancreatic ducts. In this connection von Anrep published some significant but seldom quoted experiments on pancreatic secretion. This investigator studied the simultaneous changes in the size of the pancreas and secretory rate during vagal stimulation. During early stimulation of the vagus the pancreas increased in size. At first there was no secretion of juice, but as the stimulation progressed the juice began to flow slowly and to increase gradually until it was running at a steady rate through the cannula. Simultaneously with the flow went a subsidence of the glandular edema, and at the height of secretion the gland had returned to its original size.

Edema of the pancreas under normal conditions is a temporary stage associated with vagal stimulation. This edema may be due to secretion retained in the cells or to spasm of the ducts. This normal reflex, when pushed beyond physiologic limits, could provide complete obstruction to secretory products being elaborated by the pancreas and a resultant backflow into the tissue spaces.

A further possible mechanism in obstruction is edema of the duodenal mucosa. In patients who have overindulged in alcoholic beverages, hyperemia and edema of the duodenal mucosa are common findings. The opening of the bile and pancreatic ducts into the duodenum is very small and could be closed temporarily by such swelling. Archibald demonstrated this clearly in his experimental work. Alcohol is a stimulant of both gastric and pancreatic secretion, and any obstruction of the pancreatic ducts occurring after ingestion of

this agent would lead to the development of pancreatitis. The relation of alcoholism to clinical pancreatitis has been reported by Myers and Keefer.

The cause of obstruction in patients with gallstones who do not have a stone impacted at the ampulla is not entirely clear. The most obvious explanation at hand is that in such patients spasm of the pancreatic ducts or the sphincter of Oddi is much more readily produced than in normal patients. Wangensteen and associates furnish some suggestive evidence for this view. These investigators were unable to produce mechanical blockage of the bile and pancreatic ducts by spasm in normal cats. They were, however, successful in producing obstruction by spasm in one animal that had an established infection of the gall bladder.

The degrees of pancreatitis seen clinically depend on many variables. The combination of obstruction and secretion may occur at different stages of the digestive process. The obstruction may be subacute or total. It may occur at the height of secretion or at the end.

For minimal pancreatitis or the edema as described by Elman, either temporary obstruction or total obstruction with minimal secretion can be assumed. In more advanced stages, the obstruction is prolonged. When lesions occur in the blood vessels, the obstruction has not only been of considerable duration but also the secretion has contained an appreciable amount of proteolytic enzymes. The rare case of pancreatic apoplexy occurs when a sudden complete obstruction develops to a secretion that is copious and rich in digestive enzymes. (Surgery, Oct. '48 - R. Lium and S. Maddock)

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Effect of Topically Applied Fluoride on the Incidence of Dental Caries: Previous reports in this series on the effects of topically applied fluoride on the incidence of dental caries indicate that, under the conditions of the technic of application used:

(1) A series of four topical applications of a 2-percent solution of sodium fluoride, preceded by a single dental cleansing, effects a 40-percent reduction in the incidence of dental caries. More than four applications does not increase the caries-prophylactic effect. (2) The caries-inhibiting value of topically applied sodium fluoride is not appreciably decreased during a 3-year period following treatment. (3) The omission of dental cleansing prior to a series of applications reduces the effectiveness of topically applied sodium fluoride solution by approximately half. (4) Application of a saturated solution of lead fluoride (0.06 percent), using the same technic of application as for solutions of sodium fluoride, is not associated with a significant reduction in the incidence of dental decay.

This report presents the results of seven additional studies designed to determine the possibility of increasing the caries-inhibiting effect of topically applied fluoride solutions.

During the period from May to December, 1946, groups of school children, numbering 2128 altogether and aged from 6 through 16, in Miami County, Ohio, were given applications to the teeth in half the mouth, as follows:

Group 1. Two applications of a 2-percent solution of sodium fluoride followed by the application of a 5-percent solution of calcium chloride, using a cotton applicator, and given at the rate of one or two treatments a week, without initial cleansing of the teeth.

Group 2. Two applications of a 2-percent solution of sodium fluoride followed by the application of a 5-percent solution of calcium chloride, using a cotton applicator, and given at the rate of one or two treatments a week, with initial cleansing of the teeth.

Group 3. Four applications of a 2-percent solution of sodium fluoride followed by the application of a 5-percent solution of calcium chloride, using a cotton applicator, and given at the rate of one or two treatments a week, with initial cleansing of the teeth.

Group 4. Three applications of a 2-percent solution of sodium fluoride, using a cotton applicator, and given at the rate of one treatment each 3 months, cleansing of the teeth preceding each application.

Group 5. Two applications of a 2-percent solution of sodium fluoride, using a cotton applicator, and given at the rate of one treatment each 6 months, cleansing of the teeth preceding each application.

Group 6. Two applications of a 1-percent solution of sodium fluoride, using a spray bottle, and given at the rate of one or two treatments a week, with initial cleansing of the teeth.

Group 7. Four applications of a 1-percent solution of sodium fluoride, using a spray bottle, and given at the rate of one or two treatments a week, with initial cleansing of the teeth.

In approximately half the children in each group, the teeth in the upper and lower right quadrants of the mouth were treated; in the other half of the children, the teeth in the left quadrants of the mouth were treated. The teeth in untreated quadrants served as controls. Fine pumice paste and a motor-driven rubber cup were used for cleansing the teeth. A detailed dental examination was made and the findings recorded for each of the children before treatment was begun.

The examinations were made with a No. 4 plane mirror for the mouth and a double end No. 5 explorer, under artificial light and with compressed air available for use at the discretion of the examiner. The treatment consisted of (1) isolating the teeth of the treated side with cotton rolls, (2) drying them with

compressed air, and (3) wetting the crown surfaces with the solution by using either a cotton applicator or a fine spray. The applied solution was allowed to dry in air for from 3 to 4 minutes, and then the cotton rolls were removed and the child dismissed.

In the case of the first three study groups, the crown surfaces of the teeth were wet with a 5-percent solution of calcium chloride after the solution of sodium fluoride had dried. The calcium chloride solution was also permitted to dry in air.

One year after the series of applications were begun, the children were re-examined. The data obtained indicated that:

1. The use of calcium chloride as a supplemental treatment to applications of a 2-percent solution of sodium fluoride does not enhance the caries-inhibitive action of sodium fluoride alone.

2. An increase in the spacing between applications of a 2-percent solution of sodium fluoride from once or twice a week to intervals of 3 or 6 months decreases the observed caries-inhibiting action and apparently postpones the time when the full effectiveness of four applications is operative.

3. Apparently a 1-percent solution of sodium fluoride is as effective as a 2-percent solution. However, clinical experience with the caries-prophylactic effect of a 2-percent solution is at present far more extensive than with solutions of lower concentration.

4. Application of the fluoride solution to the teeth by means of a spray appears to be as effective as when application is made by a cotton applicator. (Pub. Health Reps., 17 Sept. '48 - D. J. Galagan and J. W. Knutson)

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Circulating Anticoagulant as a Cause of Hemorrhagic Diathesis in Man: Hemorrhagic syndromes associated with defective blood coagulation have almost invariably been attributed to deficiency of one or the other of the plasma components necessary for normal clotting. The spontaneous occurrence of an anticoagulant in the circulating blood has been rarely considered to be a cause of abnormal bleeding in human patients. Quick in his extensive monograph on the hemorrhagic diseases did not mention such a condition. However, several well-studied cases have been reported in which prolongation of the clotting time and bleeding tendency have been associated with the presence of a clotting inhibitor in the circulating blood. The authors have had the opportunity to study three patients (J.H., A.V., and F.Y.) in whose blood an anticoagulant has been demonstrated.

Blood was obtained from each of the three patients using silicone-treated needles, syringes, and tubes. After centrifugation in an angle centrifuge at from 5000 to 12,000 r.p.m. for about 20 minutes, the supernatant plasma was removed. This plasma was essentially platelet-free and failed to clot even when stored for days in glass tubes. In this manner, permanently fluid native plasma was obtained without the necessity of adding anticoagulant to the blood. The presence of spontaneously occurring anticoagulant was demonstrated by adding small amounts of this plasma to freshly drawn normal human blood and observing the effect on the clotting time. For comparison an identical study was carried out on the plasma of a hemophiliac (A.B.), who had no demonstrable anticoagulant in his blood.

It was apparent that each of the three patients had a potent clotting inhibitor in his plasma. The anticoagulants in the plasmas of J. H. and of A. V. were of such a titer that one part of the patient's plasma in 100 parts of normal blood prolonged very appreciably the clotting time of the latter. In the case of F. Y., one part of the patient's plasma in ten parts of normal blood was required to produce an unequivocal delay in clotting.

A number of case reports have appeared in the literature in which atypical hemorrhagic diatheses have been found to be associated with prolongation of the coagulation time. In most of these cases the cause of the delay in clotting was not determined. For example, Madison and Quick in a recent paper describe a case and mention several others in which a hemophilia-like disease was observed in the female. In these cases no anticoagulant assay was reported. It seems not improbable that in at least some of these patients a circulating anticoagulant may have been the cause of the coagulation defect.

In 1940, Lozner et al. reported the case of a 61-year-old mulatto with a hemorrhagic disorder associated with the presence of a circulating anticoagulant. The patient was found to have a positive serologic test for syphilis and glandular tuberculosis. The source of the anticoagulant was not determined. The anticoagulant was relatively thermostabile and nondialyzable. Its effect was not altered by protamine and therefore it did not appear to be heparin. The prothrombin time was reported to be normal, so that it seems likely that the anticoagulant must have interfered with the first stage of coagulation.

A circulating anticoagulant developing in the plasma of hemophiliacs following repeated transfusions has been described by Lawrence and his associates and by Munro. Three such cases have now been reported. Study of these cases showed that the anticoagulant was associated with the gamma globulins. Craddock and Lawrence were able to demonstrate in the sera of their patients precipitins against normal plasma and against Cohn's Fraction I containing the antihemophilic globulin. They believe that the anticoagulant in the hemophiliac is an antibody against the antihemophilic globulin.

Chargaff and West reported the case of a woman with a hemophilia-like disorder in whom the prolonged clotting time was caused by a circulating anticoagulant

The anticoagulant was not inhibited by protamine. It was not antithrombic, but its effect was overcome by tissue extract thromboplastic protein. No cause for its appearance in the blood was found.

A hemorrhagic disorder in a 39-year-old female was described by Fantl and Nance. The patient was shown to have a circulating anticoagulant which appeared to be antithromboplastic for human brain thromboplastin but not for rabbit brain. There was no antithrombic activity. The bleeding tendency in this patient appeared several months after a normal pregnancy.

Castex mentioned briefly 5 cases of "pseudohemophilia" with prolonged coagulation time in which the clotting time was shortened in vivo and in vitro by protamine. He attributed the disorder to the presence of heparin in the blood. The clinical situations were not described.

The authors carried out several studies in an attempt to identify the clotting inhibitors in the blood of patients J.H., A.V., and F.Y.

The anticoagulants appeared to be different in each of the three cases. If the thesis of Craddock and Lawrence is accepted, the clot inhibitor in the hemophiliac is of antibody nature, developing as a result of therapeutic administration of a protein present in normal blood but foreign to the hemophiliac. The authors were unable to demonstrate precipitins against antihemophilic globulin in the hemophilic patient, but a relationship between previous transfusions and the production of the anticoagulant seems not unlikely. Patient J.H. whose anticoagulant resembled that of the hemophiliac in its mode of action, had not been transfused before his coagulation disorder occurred. His anticoagulant must have been produced by some other mechanism. The clotting inhibitor of A.V. was very different from the others in its mode of action. The anticoagulant in each patient was relatively heat stable, nondialyzable, and probably protein in nature.

The anticoagulants of patients J.H. and F.Y. did not appear to be antithrombic nor antithromboplastic. Their action, therefore, must precede the liberation of active thromboplastin in the blood. It seems probable that they exert their effect by preventing the conversion of a thromboplastin precursor to its active state. On the other hand, the clotting inhibitor in the plasma of A.V. definitely delayed the conversion of prothrombin to thrombin even in the presence of an excess of active thromboplastin.

The discovery of cases such as these three emphasizes the importance of carrying out anticoagulant assays on the blood of all patients with prolonged coagulation time. It seems probable that these cases are not as rare as a survey of the literature indicates. It is believed that many of the reported cases of hemophilia-like disorders could have been shown to be of this type. These cases present a serious problem with regard to therapy. The anticoagulants are so

potent that their effects obviously could not be overcome even by massive transfusions. Nothing is known which will serve as an antidote to their actions. (Bull. Johns Hopkins Hosp., Oct. '48 - C. L. Conley et al.)

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Preliminary Report on a Community-Wide Chest X-Ray Survey at Minneapolis, Minnesota: In 1947, an intensified chest x-ray survey was conducted in Minneapolis, Minnesota. The purpose was to x-ray the chest of every person 15 years of age or over, as a procedure for finding cases of tuberculosis, lung or respiratory cancer, other chest diseases, and heart abnormalities.

Eleven mobile and portable photofluorographic units for 70-mm. film were used to screen the population. In addition, one x-ray unit took 14-in. by 17-in. celluloid roentgenograms to confirm or disprove the impressions of the 70-mm. film. This report concerns the radiological findings and the first 1,500 clinical evaluations. The results of clinical study are only partially known.

Between 5 May and 25 August 1947, 306,020 70-mm. film exposures were made. Of these 4,507, or 1.5 percent, were unsatisfactory. Of the satisfactory exposures 291,275, or about 96.6 percent, were "negative" and 10,077, or about 3.3 percent, were "positive" and indicated further study.

Persons having "positive" screening film readings (except 841 of 858 showing some cardiac abnormality) were recalled for a second x-ray study with a 14-in. by 17-in. film. Of 9,236 persons recalled, 8,333 had responded by 5 January 1948.

Two thousand three hundred thirty-one, or 28 percent, of the 14-in. by 17-in. films taken were read "essentially negative," and the remaining 6,002, or 72 percent, indicated the need of further study. Of the latter 3,850, or 46.2 percent, were read as "suspected tuberculosis," and 3,627, or 94.2 percent of these, were classified concerning the stage of disease (see table below).

Impression	Number	Percent
Total	3, 627	100. 0
Minimal	3, 077	84. 8
Moderately advanced	481	13. 3
Far advanced	69	1. 9

On checking the names of the 3,850 persons suspected of having tuberculosis, on the basis of their 14-in. by 17-in. film, against the local tuberculosis case register, it was found that 3,497, or 90.8 percent, were not on the register.

For each of the persons who returned for a 14-in. by 17-in. film, an "Epidemiological Record" was prepared. In the 6,002 instances in which the radiological impression was "positive," a copy of this Epidemiological Record was submitted, for clinical study, to the individual's private physician, in 4,219, or 70 percent, of the cases, and to the public health center clinic in 1,783, or 30 percent, of the cases. The result of clinical and bacteriological follow-up was indicated on the Epidemiological Record by the doctor or clinic. Some of the information from the first 1,500 Epidemiological Records returned appears below:

	Number	Percent
Total records returned	1,500	100.0
Negative chest	159	10.6
Diagnosis tuberculosis	648	43.2
Diagnosis other chest disease	585	39.0
No diagnosis made	108	7.2

A complete breakdown of information appearing under the group of "Other Chest Disease" is not available.

It is of interest that 66 percent, or 428, of the 648 cases of tuberculosis reported on the first 1,500 Epidemiological Records were studied bacteriologically. Of the 428 so studied, 151, or 35 percent, were studied by sputum smear, 192 or 44 percent, by sputum culture and 85, or 21 percent, by culture of gastric contents. Of the patients studied bacteriologically, 79, or 19 percent, were found to be "positive" for Mycobacterium tuberculosis. In addition to these 79 cases classed as active on the basis of bacteriological study, there were 19 cases considered active on the basis of x-ray changes and clinically consistent with active tuberculosis.

The stage and activity of disease of the 648 persons diagnosed as having tuberculosis are shown in the table below. Of the 98 active cases of tuberculosis,

	Total		Minimal		Moderately advanced		Far advanced		Other	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	648	100.0	463	100.0	121	100.0	23	100.0	41	100.0
Active	98	15.1	39	8.4	49	40.5	9	39.1	1	2.4
Questionably active	17	2.6	10	2.2	6	5.0	0	0.0	1	2.4
Inactive	533	82.3	414	89.4	66	54.5	14	60.9	39	95.1

nine were previously registered with the Minneapolis Health Department. Of these nine, six were being carried on the active register and three were being carried on the inactive register. An additional nine persons with active tuberculosis admitted a history of the disease but were not known to the health

department. Eighty represented new cases of tuberculosis. Of these, 25 had neither contacts nor symptoms. The disease could have been found only with case-finding methods such as roentgenological study, or tuberculin testing on a mass basis. The remaining 55 out of 80 new patients had signs or symptoms. It may be supposed, but there is no assurance, that these were related to their tuberculosis. Apparently the signs or symptoms were not severe enough to cause the individuals to seek medical attention. Only three reported that they had been in contact with a case of tuberculosis. Of the 80 new cases of tuberculosis discovered, only three could have been found through contact examination, providing the contact had occurred in their place of residence or had been reported to it.

As of 15 February 1948, 55 of the 98 persons with active tuberculosis had entered a sanatorium. The stage of their disease was minimal in 30.9 percent, moderately advanced in 56.4 percent, and far advanced in 12.7 percent. (Pub. Health Reps., 1 Oct. '48 - W. Roemmich et al.)

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Study on the Affinity of Neoplastic, Embryonic, and Traumatized Tissues for Porphyrins and Metalloporphyrins: In the course of studies on the cocarcinogenic action of porphyrins, tumors developed in many of the mice that had been given injections of methylcholanthrene and porphyrins. When these mice died or were sacrificed, it was noted that the porphyrin which had been injected intraperitoneally had accumulated in the subcutaneous sarcomas to such a degree that the tumor had become red fluorescent but other normal tissues had not. A search of the literature revealed that other investigators had also observed the tendency for injected hematoporphyrin to accumulate in neoplastic tissues of rats. They had, however, only recorded this observation without further attempts to study or interpret this phenomenon. The affinity of porphyrins for neoplastic tissue was so striking that the authors studied this in some detail. It was realized at the outset that if this affinity of neoplastic tissues for porphyrins extended also to metalloporphyrins and thus to radioactive metalloporphyrins, and proved to be generally true for all tumors, then this class of substances could be utilized to improve the existing methods of cancer detection and therapy.

The present report is based on observations made on 240 tumor-bearing and 50 nontumor-bearing mice. The neoplasms studied included methylcholanthrene-induced tumors (spindle-cell fibrosarcomas and rhabdomyosarcomas), transplanted fibrosarcomas, spontaneous mammary carcinomas and transplanted mammary adenocarcinomas (variable type). The observations on the first 30 mice were nonsystematic and extended over a period of about 2 years. In the first systematic experiment the tendency of all available types of mouse neoplasms to concentrate hematoporphyrin was tested. Eighty mice were used in this experiment. Forty of these bore tumors of one of the types mentioned

above. Twenty tumor-bearing and 20-nontumor-bearing mice were given intraperitoneal injections of 1 mg. of hematoporphyrin. Eight of these mice in which hematoporphyrin had been injected and 8 controls which had been given no injections were sacrificed at 24-hour intervals to determine the rate of development of maximum concentration of hematoporphyrin in the tumors. Most of the porphyrin injected was concentrated in the tumor within a period of from 24 to 48 hours. Some of the porphyrin was eliminated through the liver and appeared in the red fluorescent feces. The greater omentum became red fluorescent and remained so for several days. Lymph nodes also became red fluorescent in all mice. Hematoporphyrin does not become concentrated in the other tissues. Carcinomatous or sarcomatous mice in which hematoporphyrin had been injected, when sacrificed at the end of 24, 48, or 72 hours, exhibited brilliant red fluorescent tumors in contrast to the tumors of the controls.

These phenomena were observed several times and in subsequent experiments it was established that the porphyrin concentration as indicated by the red fluorescence of the tumor remains high for from 10 to 14 days but gradually decreases. If the tumors contained necrotic centers, the concentrations of porphyrin were greatest in and near such areas. Hematoporphyrin was concentrated in all types of tumors tested. This indicated that the affinity of the tumors for porphyrin was not specific but perhaps general for all tumors.

Since regenerating and embryonic tissues are similar in some respects to neoplastic tissues, it was desired to know whether porphyrins would also be concentrated in these tissues. The injection of hematoporphyrin into pregnant mice revealed that much of the porphyrin accumulated in the placentas and in the embryos. When hematoporphyrin was injected into mice which had been incised or otherwise traumatized, the porphyrin became concentrated at the site of injury and near the regenerating margins of incisions. These experiments indicated that growing tissues in general have an affinity for hematoporphyrin.

It is therefore probable that all neoplasms have an affinity for porphyrins similar to that observed for this limited number of mouse tumors. It was known from the numerous observations in the experiments on cocarcinogenesis that neoplastic tissue had an affinity for both hematoporphyrin and protoporphyrin but it was desired to know whether this extended to other porphyrins. Mesoporphyrin and coproporphyrin were also tried and these substances also were concentrated in neoplastic tissue. At the pH of the tissues the intensity of fluorescence of protoporphyrin and coproporphyrin is not as great as that of hematoporphyrin and the concentrating effect does not seem as spectacular. A number of other fluorescent substances (fluorescein, rhodamine, dihydrocollidine and riboflavin) were also tested and for none of these was the same affinity exhibited by the tumors.

Perhaps the most important question was whether the neoplastic tissues would have the same affinity for metalloporphyrins. Heme (iron-protoporphyrin)

was tested intensively, but no conclusions could be drawn because the heme does not fluoresce and therefore could not be distinguished easily from hemoglobin and other substances present in tumor tissues. Zinc hematoporphyrin was therefore prepared, and it was found that it, in contrast to heme and many other metalloporphyrins, fluoresces with a characteristic spectrum and can easily be traced through the bodies of mice. A repetition of the experiment described above using 10 mice bearing transplanted methylcholanthrene-induced sarcomas demonstrated that the zinc hematoporphyrin also accumulated in tumor tissues. Even though the intensity of fluorescence of this compound is not as great as that of hematoporphyrin at the pH of the tissues, it was possible to observe visually the spectrum of fluorescence of this compound in tumor tissues, but not in adjacent normal tissues.

The tendency of injected porphyrins and metalloporphyrins to accumulate in lymph nodes may limit the therapeutic usefulness of these compounds in all neoplastic diseases except lymphatic leukemias. The possibility of using small doses of radioactive metalloporphyrins for detecting deep cancer is being investigated. (Proc. Soc. Exper. Biol. and Med., July-Aug. '48 - F. H. J. Figge et al.)

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The Problem of Cross-Eyes: Under the sponsorship of the Office of Naval Research, a project is being carried out at Washington University's School of Medicine, St. Louis, on the basic factors which influence heterophoria (a tendency of one eye to deviate in one or another direction as a consequence of imperfect balance of the ocular muscles).

When a child is born with, or later develops, cross-eyes, many parents will at first refuse to admit and even refuse to see that their child is cross-eyed. Once the parents fully recognize the child's plight, they set out for advice, usually in the hope of an immediate cure. Much of the advice given about cross-eyes is, unfortunately, bad. For instance, the advice that a child will "outgrow" his cross-eyes is vicious information that has already done incalculable damage and will do much more unless discontinued. A consideration of facts reveals that hardly one in a thousand truly cross-eyed children ever "outgrows" his defect in the absence of any treatment.

The occurrence of cross-eyes in families has long been known. Just as certain facial characteristics can be passed on from one generation of a family to the next, so may certain anatomic anomalies which predispose to the development of cross-eyes be inherited. At least 90 percent of the children whose eyes cross before they reach the age of six have some abnormality of the muscles which move their eyes. Although these abnormalities are seldom severe enough to cause the eyes to cross in the absence of other causative factors, they nevertheless play a prominent part in causing cross-eyes when combined with other factors quite commonly found in the child's environment.

All babies, at birth, are farsighted. In the normal course of events, a child outgrows his farsightedness (hyperopia) and at about the age of eight reaches "normality" with respect to his eyes. If the growth of the eyes lags behind that of the rest of the body, or stops prematurely, the child remains farsighted for the rest of his life. Farsightedness means that it requires less effort for objects to be seen at a distance than at the usual reading distance. The farsighted person frequently has normal vision in the sense of being able to see "20/20" or even "20/15" and yet it requires extra effort on his part to secure normal vision. This extra effort is in the form of focussing power or accommodation. In the normal individual, when an object close at hand is observed, two things must happen if it is to be seen clearly: (1) each eye must focus accurately (accommodate) on the object, and (2) each eye must look directly at it (the visual axes of the eyes must converge). There is, therefore, a close association between convergence and accommodation (focussing). The farsighted person has to focus (accommodate) more than the normal person in order to see clearly; in the process of accommodating more than the usual amount, there is a coincident tendency to converge more than the usual amount as well. It is this tendency to over-converge, because of the necessity for extra accommodation in the farsighted person, that precipitates the crossing of many children's eyes at about the age of from two and a half to three. Over 50 percent of cross-eyed children are farsighted. They do not develop sufficient focussing powers (accommodation) to overcome their farsightedness until about the age of from two and a half to three, and hence their eyes do not cross until they reach that point in life. It may be concluded, therefore, that farsightedness is a precipitating cause, but not the whole cause, of cross-eyes in a majority of children.

Farsightedness can be corrected with glasses, which eliminate the need for excessive focussing. This in turn eliminates the tendency toward over-convergence. If the crossing of the eyes is due to farsightedness entirely, glasses will straighten the eyes completely. If farsightedness is only a precipitating cause, not the entire cause, glasses will straighten the eyes only partially; the remainder of the crossing requires correction by other methods. Thus, many children with cross-eyes have the angle of the crossing markedly reduced when wearing glasses, but the eyes may still not be entirely straight.

The muscle inside the eye which is used for focussing is the ciliary muscle. If an individual is farsighted, he must focus excessively if he is to see clearly. In the process of constantly focussing more than is usual, the ciliary muscle becomes excessively strong in order to compensate for the farsightedness. If the ciliary muscle, by excessive contraction, can partially or completely neutralize the farsightedness, then it is obvious that this muscle must be forced to relax completely in order that the farsightedness may be measured accurately, and appropriate glasses given. Proper relaxation of the ciliary muscle in farsighted children is seldom if ever attained unless some relaxing drug is instilled in the eyes. This is the reason that the ophthalmologist should insist on using atropine prior to his examination of a cross-eyed child to determine the amount of farsightedness present.

A child learns to use his two eyes together in fusion at the age of about five and a half years. If the child with cross-eyes can have them straightened before he finally learns to fuse, he may learn to use his eyes together normally in binocular single vision (fusion), which is the ultimate goal in all cases of cross-eyes. Otherwise, he will have to learn to get along with his defect. He will be able to do this, but in an abnormal way. Therefore, every cross-eyed child should have his defect corrected before he reaches the critical fusion-development age of about five and a half years.

Cross-eyedness very often makes the child a target for nicknames and unkind remarks from his playmates. His normal development is impossible under such circumstances. Two courses are available; the cross-eyed child may withdraw from the group, feeling keenly his difference from the others, to become shy, introverted, and retiring, with a feeling of inferiority; or drop back to a younger group of children where, because he can feel superior to others on the basis of his advanced age and physical development, he compensates by becoming a bully. By the time a cross-eyed child begins kindergarten it appears that some damage has been done to the psyche; at the end of the first year of school, there is no question about the situation. It is vital, therefore, that cross-eyes not only should be corrected before a child is five and a half, but also before he begins school.

If the normal person crosses his eyes voluntarily, he will see double. The cross-eyed person, however, never sees double. Instead, he uses only one eye. In some types of cross-eyes, the child may use first one eye and then the other, but never both together as a team. In other types, the child always uses only one eye, and the opposite eye always crosses. In the former type, the vision usually remains equal in the two eyes. In the latter, the eye which always crosses slowly loses vision and thus may become quite useless. Before the child can learn to fuse, this lost vision must be regained and, fortunately, it will return if the child is forced to use the "weak" eye. The only way a child can be forced to use one eye is to cover the other eye with a patch. This patching of the good eye should be constant in order that vision may be restored as quickly as possible, because time is vital. The patch should be placed over the eye the moment the child awakens in the morning and kept on the eye until he is ready to go to sleep at night. The sooner vision can be restored in the "weak" eye, the sooner a cure may be affected.

If glasses have been given, and if vision has been restored in the "weak" eye by patching, and the eyes are still not straight, then an operation is almost invariably required to complete the cure. It is only the patient whose eyes are crossed very slightly when wearing glasses that can be cured by eye exercises alone, without surgery.

Eye exercises are widely used, and unfortunately often enough are misused. In the first place, eye exercises do not strengthen weak muscles. Their sole aim is to teach the child to use his two eyes together as a team (to fuse). Nothing

is more hopeless than a child whose eyes are markedly crossed taking expensive exercises week after week, in the hope that the eyes will miraculously become straight with exercises alone. Judiciously employed preliminary to, or after, an operation exercises are often invaluable. However, such exercises must be employed intelligently, under the guidance of an experienced orthoptic technician or they may do more harm than good. (Research Reviews, 15 June '48 - R. G. Scobee)

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Recent Developments in the Treatment of Syphilis: Most syphilitics can now be treated satisfactorily with penicillin alone, but occasional patients may require the use of bismuth, arsenicals, or fever therapy.

At least 2 years of follow-up observations are required for the proper evaluation of any schedule of antisyphilitic treatment; and in spite of careful planning, the optimum time of penicillin treatment for early syphilis has not yet been thoroughly established. There is now adequate information regarding the optimum total dosage of penicillin for the treatment of early syphilis within 8 days, but the data on more prolonged periods of treatment are still in the process of compilation. The time-dose relationships of therapy with aqueous solutions of penicillin are very different from those with slowly absorbed preparations. The introduction of penicillin in oil and beeswax (POB) made it possible to treat syphilis with single daily injections, but most of the data on prolonged follow-up studies of patients treated for early syphilis with POB concern 8-day schedules of therapy. Furthermore, within the past few months, preparations of penicillin which are even more slowly absorbed than POB have become available, with the result that a still wider range of possible time-dose relationships in the penicillin treatment of syphilis now exists. The data are not yet sufficiently complete to give final conclusions about optimum schedules of therapy with the new preparations.

Penicillin in aqueous or saline solution. Crystalline penicillin G has been used almost exclusively since the latter part of 1946 because it is one of the most effective of the known penicillins and can now be manufactured in almost pure form.

In aqueous or saline solution, sodium, potassium, and calcium salts of penicillin are rapidly absorbed after injection and rapidly excreted. For continuous effect, individual injections of from 20,000 to 80,000 units must be given from every 2 to 4 hours. In most of the clinical research on the treatment of syphilis with aqueous solutions of penicillin, the patients were given individual injections every 3 hours, but many others were also treated at 2-, 4-, and 6-hour intervals. When individual injections of from 30,000 to 90,000 units were given, it made no significant difference in the treatment of early syphilis whether injections were given at 2- or 6-hour intervals, provided a total dose of at least 2.4 million units

was used in a period of 7 and 1/2 days. The minimum period during which penicillin must be active within the body for the cure of early syphilis in a fairly high percentage of cases seems to be about 4 days. By giving very large doses of penicillin in aqueous solution, the absorption and excretion can be appreciably delayed. Early syphilis has been treated with 200,000 units of penicillin in aqueous solution every 2 hours for 36 injections (a total of 7.2 million units in 3 days). The results, so far, seem to be comparable with those obtained with a total dose of 2.4 million units over 7 and 1/2 days. But, regardless of whether very large total doses are injected for 3 or 4 days or smaller doses are given over a longer period, the use of penicillin in aqueous solution requires frequent injections which makes it impossible to treat patients on an ambulatory basis.

Penicillin in oil and beeswax (POB). When large particles (50 microns or more) of penicillin G are mixed with oil and 4.8 percent beeswax, the presence of penicillin in the blood can be demonstrated for from 20 to 30 hours after a single injection of 300,000 units. The introduction of this preparation made it unnecessary to give individual injections more than once a day. The author's experience at Bellevue Hospital indicates that, when total doses of from 2.4 to 4.8 million units of POB are used over a period of 8 days, single daily injections of from 300,000 to 600,000 units are as effective as smaller individual doses given more frequently, and the results of treatment are comparable with those obtained with similar total doses of penicillin in aqueous solution.

Procaine penicillin G in oil. Procaine penicillin G in oil, available since early in 1948, so far, has been proved to be the most practical of the slowly absorbed salts. A single injection of 300,000 units of this preparation gives demonstrable blood concentrations of penicillin for from 20 to 30 hours as does a similar dose of POB. Procaine penicillin in oil, however, has the advantage of being more easily administered than POB and, to date, fewer local and generalized reactions have resulted from its use.

Procaine penicillin G in oil and 2-percent aluminum monostearate. Soon after the production of procaine penicillin G in oil, it was found that the absorption of penicillin could be still further delayed by adding aluminum monostearate to the penicillin-oil mixture. Aluminum monostearate is a water-repellent substance which coats the particles of penicillin and greatly delays absorption. When procaine penicillin G is mixed with oil, penicillin particles of 50 μ or over are needed for delayed absorption. When aluminum monostearate is added to the mixture, small particles of penicillin are absorbed even more slowly than large particles. At Bellevue Hospital and elsewhere, numerous different penicillin preparations were investigated in cooperation with the Bristol Laboratories. The preparation of procaine penicillin in oil and 2-percent aluminum monostearate was found to give the most prolonged blood concentrations. Following a single injection of 300,000 units, demonstrable blood concentrations of the antibiotic were found for 4 days or more

in about 90 percent of 168 cases. Following injections of from 1.2 to 2.4 million units, blood concentrations of penicillin were found for about 5 days in most cases; and in some instances penicillin was demonstrated in the blood for as long as 7 or 8 days after the injection.

Obviously the availability of penicillin preparations which are slowly absorbed for from 4 to 7 days following a single injection still further simplifies the treatment of syphilis. High peaks of penicillin in the blood apparently mean very little in the treatment of syphilis. Many patients with early syphilis can be cured with little or no demonstrable blood concentrations of penicillin, provided there is fairly continuous action of penicillin over a sufficiently long period. Consequently, preparations which give continuous blood concentrations of the antibiotic for 4 or more days make it unnecessary to give daily injections, and possibly weekly injections of from 1.2 to 2.4 million units would suffice.

At present it is impossible to give data on the treatment of syphilis with procaine penicillin in oil and aluminum monostearate. Nevertheless it is reasonable to believe that the experience with aqueous solutions and POB can be used to estimate the time-dose relationships of treatment with preparations which give more prolonged absorption of penicillin.

Results of Treatment of Early Syphilis with Aqueous Solutions of Penicillin. Abundant data are now available to show that, when individual injections of penicillin in aqueous solution were given from every 2 to 4 hours over a period of 7 and 1/2 days, a total dose of 2.4 million units has given as good results as 5 million units. The addition of daily injections of 0.04 Gm. arsenoxide for 8 days to total doses of from 1.2 million to 2.4 million units of penicillin failed to give significantly better therapeutic results than 2.4 million units alone in 7 and 1/2 days.

The cumulative "failure" rates for all schedules of therapy of early syphilis with aqueous solutions of penicillin in total doses of from 2.4 to 4.8 million units in 7 and 1/2 days have been about 20 percent. The "failure" rates were computed on the basis of the number of patients kept under observation; the "failures" included all patients that had to be re-treated because of reinfection, infectious relapse, serologic relapse, and definite seroresistance.

Failure rates of 20 percent in the treatment of early syphilis are not satisfactory, but many of the so-called failures were probably reinfections. Therefore, it is impossible to judge the effects of the treatment of early syphilis solely from statistics based on the re-treatment of patients. The only satisfactory criterion of a reinfection following rapid treatment of early syphilis is the development of a new chancre at a different site from the original one, and even this criterion was not used in compiling these cumulative "failure" rates. Had it been used, the percentage of "failures" would be somewhat lower, but unfortunately patients can be reinfected following rapid treatment of early syphilis

without developing a chancre. Less than 50 percent of women who are originally infected with syphilis have chancres which are observed by the patient or examining physician. The appearance of secondary lesions may be the first observed sign of a reinfection in both women and men, and in some cases the only evidence of a reinfection may be a rise in the quantitative units in the serologic tests for syphilis (serologic relapse). Thus, the actual effects of treatment with aqueous solutions of penicillin were undoubtedly better than the statistics indicate. Nevertheless, the treatment of early syphilis with aqueous solutions of penicillin over periods of from 4 to 8 days has not produced maximum therapeutic results, and there are no comparable data on more prolonged periods of therapy with aqueous solutions.

Results of Treatment of Early Syphilis with POB. Although injections of from 300,000 to 600,000 units of POB do not have to be given more frequently than once a day, the total dosage of penicillin required for the treatment of syphilis over a given period of time seems to have been much the same, whether the penicillin was given in aqueous solution or in oil and beeswax. At Bellevue Hospital in the latter part of 1945 and early months of 1946, over 800 patients with early syphilis were treated with 600,000 units of POB daily for 8 days. One series was treated with two injections of 300,000 units 8 hours apart each day, and another series with single daily injections of 600,000 units There was no significant difference in the results of treatment in the two serie. . Whether a total dose of 2.4 or 4.8 million units is given over 8 days, the available data indicate that the cumulative "failure" rates are much the same. In the series of patients treated for 8 days with 4.8 million units of POB, the cumulative "failure" rates for a follow-up period of 2 years or more are similar to those for 2.4 million units of penicillin in aqueous solution in 7 and 1/2 days, viz., about 20 percent.

Data on 15-day schedules of penicillin therapy for early syphilis cannot yet be compared satisfactorily with those on 8-day schedules because of the marked difference in the time of follow-up observations and the varying conditions under which patients were treated.

At Bellevue Hospital a series of patients with early syphilis was treated with daily injections of 600,000 units of POB for 15 days late in 1947. The series so treated is not entirely comparable with earlier series because the reservoir of infectious syphilis was appreciably lower in the latter part of 1947 and first half of 1948 than in the preceding 4 years. The chances of reinfection by promiscuous individuals is greater when the reservoir of infectious syphilis is high than when it is low.

But, in spite of uncontrollable variables, a 15-day schedule of therapy for early syphilis now seems superior to one of 8 days. At Bellevue Hospital, of 134 patients treated for early syphilis with 600,000 units of POB daily for 15 days and observed for from 4 to 9 months, only 2 have had to be re-treated and both of them were probably reinfected. It is quite possible that daily injections

of 300,000 units of POB would have given results similar to those from 600,000 units daily. Chargin, Sobel, Rein, and Rosenthal have reported relapses after a follow-up period of from 6 to 10 months in less than 5 percent of patients treated for secondary syphilis with 300,000 units of POB daily for 16 days.

Possible Schedules of Treatment of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate. Because single injections of from 300,000 to 600,000 units of procaine penicillin G in oil and 2-percent aluminum monostearate give blood concentrations of penicillin for about 4 days, daily injections of this preparation should be unnecessary in the treatment of syphilis. A Committee on Venereal Diseases of the National Institute of Health is now studying the treatment of early syphilis with the following schedules of therapy using procaine penicillin in oil and aluminum monostearate:

1. A single injection of 2.4 million units
2. Weekly injections of 1.2 million units for 2 weeks
3. Weekly injections of 1.2 million units for 4 weeks.

The use of schedule 1, although it cannot be advised as yet, should give results very similar to those obtained by injections of 40,000 units of penicillin in aqueous solution every 3 hours for 60 injections or of daily injections of 300,000 units of POB for 7 or 8 days. The optimum period of treatment for early syphilis now seems to be 15 or more days. Therefore, schedules 2 and 3 are likely to give better results than schedule 1.

Other possible schedules of treatment with procaine penicillin in oil and aluminum monostearate are injections of 600,000 units two or three times a week for from 2 to 3 weeks. At least another 2 years or more will be required before one can state with assurance the optimum time during which penicillin should be given in the treatment of early syphilis, but at present it does not seem likely that treatment need be given for more than from 2 to 3 weeks.

Response of Serologic Tests for Syphilis Following Rapid Treatment of Early Syphilis. The goal of therapy in the treatment of early syphilis is cure, with the achievement of seronegativity by all patients. Serologic tests for syphilis (STS), however, do not become negative immediately after treatment. At Bellevue Hospital, about 80 percent of patients satisfactorily treated for seropositive primary syphilis became seronegative within six months after treatment; and only about 60 percent of those satisfactorily treated for secondary syphilis became seronegative within 6 months after treatment. The remaining 20 and 40 percent respectively required varying periods before the STS became completely negative. Some patients had small amounts of reagin in the blood for more than 2 years after treatment, but in such cases the quantitative tests showed relatively low titers within 6 months after treatment. The prolonged presence of small amounts of reagin in the blood for many months after treatment for early syphilis does not necessarily mean a continuing syphilitic infection because it was found that re-treatment did not hasten the reversal of such

positive tests to negative and that in the course of time the STS became negative without further therapy unless a relapse occurred.

At Bellevue Hospital the more or less arbitrary rule was made that patients who have positive Kahn tests in dilutions of 1-8 or quantitative complement-fixation tests of 15 or more 9 months after treatment should be re-treated. Very few patients treated for early syphilis will have such relatively high quantitative STS 9 months after treatment unless they have relapsed. Relapse is detected either by the appearance of new early lesions or by marked, sustained rises in quantitative STS from previous levels.

Treatment of Relapsing Early Syphilis. At Bellevue Hospital the cumulative "failure" rates of patients re-treated for "relapsing" early syphilis with at least 2.4 million units of penicillin in 8 days have been about 20 percent. Many of these patients probably had reinfections rather than relapses. In cases of genuine relapse it is advisable to treat over a longer period than 8 days. A few of the patients had to be re-treated two or three times for repeated relapses, but there have been no absolute failures in the entire series. For a first relapse, patients should be re-treated with no less than 6 million units of penicillin over a period of at least 15 days. Those who relapse a second time should receive 9 million units over a period of at least 21 days. Rarely it may be advisable to supplement the penicillin therapy with arsenicals and bismuth. In such cases, the author believes the treatment with arsenicals and bismuth should be given after the course of penicillin has been completed. This procedure prolongs the therapy and may be more effective than combining the arsenicals and bismuth with penicillin therapy over a period of only 2 or 3 weeks.

Treatment of Late Neurosyphilis with Penicillin. In the experience of Bellevue Hospital, fever therapy (malaria or electropyrexia) caused permanent arrest of neurosyphilis, as determined by spinal fluid examinations, in about 85 percent of cases and, so far, penicillin has proved superior even to fever therapy in the treatment of all types of neurosyphilis, including general paresis.

During the first three years of trial with penicillin, some investigators reported, on the basis of clinical response, that fever therapy was superior to penicillin in the treatment of general paresis, and maintained that the best therapy was a combination of penicillin and fever. At Bellevue Hospital, Dattner and the author have long contended that the most reliable guide to the arrest of a syphilitic infection of the central nervous system is the spinal fluid examination. Following successful therapy, the cells in the spinal fluid should be less than 4 per cu. mm. from 3 to 4 months after treatment, and there should be an appreciable fall in the figures obtained for increased total protein. Over a prolonged period of observation, the figures determined for the total protein in the spinal fluid should fall to normal, and the colloidal gold and quantitative Wassermann tests should gradually become negative. In some of the malaria-treated cases at Bellevue the Wassermann reactions of the spinal fluid failed to become negative for more

nan 5 years after treatment but, as long as increased total protein determinations were falling and quantitative Wassermann and colloidal gold tests were declining toward negative reactions, it was not found that further antisyphilitic treatment helped to improve clinical symptoms and signs which are caused by permanent damage in the central nervous system.

Most investigators have now agreed that the response of the spinal fluid tests following penicillin therapy of neurosyphilis has been as good, if not better than, the response after fever therapy, and numerous authorities have stated that the clinical improvement after penicillin was comparable to that after fever therapy. In England, both Nicol and Martin, who have had much experience with malaria therapy of general paresis, have reported that penicillin is superior to fever therapy.

It must always be recognized that no spirocheticidal agent can replace scar tissue with functioning parenchyma. Consequently, in cases of advanced neurosyphilis it is frequently impossible to restore normal function in spite of the total arrest of a syphilitic infection. Therefore, the spinal fluid tests furnish a better guide to the effectiveness of treatment of neurosyphilis than clinical signs and symptoms.

On the basis of follow-up spinal fluid examinations, 88.3 percent of 301 patients treated at Bellevue Hospital for various types of neurosyphilis with penicillin alone and followed up for from 9 to 48 months had satisfactory results after treatment with from 2 to 9 million units of penicillin given over a period of from 12 to 20 days. Most of the patients who had to be re-treated received less than 6 million units of penicillin at the time of their first treatment. So far, only 1 patient has failed to respond satisfactorily after a second course of penicillin. Among the patients who had satisfactory results after penicillin therapy were 5 who had had much previous treatment with malaria therapy, bismuth, and pentavalent arsenicals. Because the author and associates have observed over 500 patients treated at Bellevue Hospital for neurosyphilis with malaria and electropyrexia in previous years, the author has no hesitancy in stating his belief that penicillin has proved superior to fever therapy in the treatment of neurosyphilis, including general paresis.

Schedules of penicillin therapy for neurosyphilis. From experience at Bellevue Hospital, late neurosyphilis should be treated with no less than 6 million units of penicillin over a period of at least 15 days and preferably 3 weeks. Most of the patients were treated with 40,000 units of penicillin in aqueous solution every 3 hours for 150 injections (19 days). More recently, neurosyphilis has been treated with daily injections of 600,000 units of POB for 15 days. With the use of procaine penicillin in oil and aluminum monostearate, it is probable that injections of 600,000 units three times a week for 3 weeks will give comparable results with those from 40,000 units of penicillin in aqueous solution every 3 hours for 150 doses.

Treatment of Late Symptomatic Syphilis Other Than Neurosyphilis. The data on penicillin treatment of late symptomatic syphilis, other than neurosyphilis, are less abundant than on the treatment of early syphilis and neurosyphilis. Nevertheless, except for two reports of gummas which failed to respond to penicillin, all types of late syphilis have responded well to penicillin therapy. Of 26 patients with late bone syphilis and cutaneous lesions treated at Bellevue Hospital with penicillin and observed for more than 2 years, all had satisfactory healing and none had relapsed.

To avoid Herxheimer reactions in cases of cardiovascular syphilis and syphilis of the liver, it is advisable to begin treatment with bismuth, but after several weeks of bismuth injections, the treatment can be completed with penicillin. Although the published reports of penicillin therapy of cardiovascular and hepatic syphilis include relatively small series of patients, the results of treatment have been as satisfactory as could be expected.

Schedules of penicillin treatment of late symptomatic syphilis. From the data now available, late symptomatic syphilis, other than neurosyphilis, should be treated with from 4 to 6 million units of penicillin over a period of not less than fifteen days. If procaine penicillin G in oil and aluminum monosterate is used, injections of 600,000 units two or three times a week for 3 weeks should prove to be adequate therapy in most cases.

Treatment of Late Latent Syphilis. By definition, late latent syphilis is asymptomatic; it is diagnosed solely by history and positive STS. (The spinal fluid must have been examined in all cases of latent syphilis and found to be normal before the diagnosis can be made.)

Because the STS do not become negative in most patients treated for late syphilis for many years after treatment, it is difficult to evaluate the effects of therapy in latent cases. Obviously, however, the kind and amount of antisyphilitic treatment which has proved effective in late symptomatic syphilis should be adequate for the treatment of late latent cases.

In the follow-up of patients treated for late latent syphilis quantitative STS should be obtained at regular intervals. As long as the quantitative tests show a gradual trend toward negative reactions or fail to show marked, sustained rises from previous levels, further antisyphilitic treatment is not advised. The policy of treating late syphilis, symptomatic or asymptomatic, until the STS have become completely negative cannot be too strongly condemned. At least 70 percent of patients treated for late syphilis with any known form of antisyphilitic therapy will continue to have positive STS for more than 5 years after treatment, and some will continue to have positive STS for the rest of their lives. To treat patients for late syphilis with the sole purpose of reversing positive STS to negative is a serious error; it involves misrepresentation to the patient because there is no evidence that continued antisyphilitic therapy will in any way hasten the

reversal of positive STS to negative in well treated cases. Late latent syphilis can, in most cases, be satisfactorily treated with from 4 to 6 million units of penicillin over a period of from 2 to 3 weeks. (Am. J. Pub. Health, Oct. '48 - E. W. Thomas)

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Disposal of Used Fluorescent Lamps: The Technical Advisory Committee on Beryllium, appointed during the past year by an executive committee representing the beryllium industry, has issued a list of precautions to be observed in disposing of used fluorescent lamps, especially in large quantities, on account of the possible hazard of exposure of human beings to beryllium compounds. The lamps are coated inside with a "phosphor" which contains up to 4-percent beryllium; the lamps also contain small amounts of mercury. In addition to inhalation of the dust, another hazard arises from cutting of the skin by broken glass, introducing the phosphor dust which may lead to chronic inflammation. It is recommended that all used lamps be broken before disposal, and that no attempts be made to salvage the used phosphors. Recommendations are made to cover two general situations. In both, goggles should be worn and protection from flying glass should be maintained.

Situation 1. This covers the breaking of a small number of fluorescent lamps daily or intermittently during which there is exposure of the operator for a matter of minutes only: (a) break all tubes out of doors in a waste disposal area or in a waste container; (b) avoid breathing dust and vapors that may evolve.

Situation 2. This covers the breaking of large numbers of fluorescent lamps, either intermittently or regularly, in which hours may be occupied in the operation: (a) break lamps out of doors in waste disposal area or in ventilated hood (to avoid unnecessary dust, the breakage is best done within the waste container); (b) the operator should be supplied with, and required to wear, a respirator approved by the United States Bureau of Mines for toxic dusts; (c) ultimate disposal of the broken lamps should be such that the public and others will not be unduly exposed to powders.

In situations in which it is necessary to break lamps within buildings, it should be done by the operator in an isolated room and under a hood, in order to minimize escape of dusts. Sufficient exhaust ventilation should be supplied to the hood to provide an air intake of at least 125 linear feet per minute at the breathing level. (Conn. Health Bull., Aug. '48, through Indust. Hyg. Digest, Sept. '48)

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Course in Aviation Medicine: The next course in aviation medicine will be given at the School of Aviation Medicine and Research, U. S. Naval Air Station, Pensacola, Florida, beginning 17 January 1949.

The course of instruction is divided into two phases. In the first phase, five months of instruction are given in the subjects of applied aviation physiology, otolaryngology, ophthalmology, psychiatry, cardiology, and other subjects applicable to aviation medicine. In the second phase, students are assigned to flight indoctrinational training and ground school work. Upon successful completion of the entire course of training, the student is designated a naval flight surgeon.

It should be pointed out that a vast amount of research in aviation medicine will be required in support of the current research program. Moreover, it is essential that flight surgeons be trained to replace those being assigned to duty under instruction in the various clinical fields.

Applications are desired for the course in aviation medicine from medical officers of the regular Navy, and from medical officers of the Naval Reserve who have at least two years of obligated service. Applicants should be of the rank of lieutenant commander or below.

Applications may be made by dispatch and must reach the Bureau of Medicine and Surgery prior to 10 December 1948. (Professional Div., BuMed)

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Armed Forces Staff College Course Available to Medical Officers: The courses at the Armed Forces Staff College, Norfolk, Virginia, begin in February and September of each year and continue for a period of 5 months. Two medical officers of the Navy may be assigned to each of the courses scheduled for 1949.

The scope of instruction includes orientation, organization, characteristics, and employment of Army, Navy, and Air Forces and the relation of these forces to one another; the study of joint staff technics and procedures, the preparation of plans for amphibious and airborne operations involving the employment of joint forces; and also the study of the organization, composition, and functions of theater and joint task forces and responsibilities (strategical, tactical, and logistical) of the commanders thereof.

Assignment to the Armed Forces Staff College course involves a permanent change of station, entitling the officer to transportation costs for dependents and household effects. Quarters are furnished on the station for all students (family quarters for married officers and BOQ for bachelors).

The completion of this course of instruction qualifies the officer for billets on the staff of fleet and area commanders, etc., and for duty in the logistical field.

Applications for these courses are desired from commanders and lieutenant commanders of the Medical Corps of the regular Navy. (Personnel Div., BuMed)

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BUMED CIRCULAR LETTER 48-115 21 October 1948

To: Commandants, NavDists (Continental)
NavHosps (Continental)
SubBase, New London, Conn.
NAS (Atlanta, Ga.; Dallas, Tex.; Glenview, Ill.; Grosse Ile, Mich.; Lambert Field, St. Louis, Mo.; Miami, Fla.; Olathe, Kans.; Patuxent River, Md.; Seattle, Wash.)
NavSta (New Orleans, La.; Orange, Tex.; Tongue Point, Ore.)
NavOrdPlant, Pocatello, Idaho

Subj: Naval and National Cemeteries; List of

Ref: BuMed CirLtr 47-151, 7 Nov 1947.

In this letter it is stated that Fort Rosecrans National Cemetery, San Diego, California, has been added to the list of National cemeteries in which the remains of those who have had honorable service in the Navy and Marine Corps may be buried.

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BUMED CIRCULAR LETTER 48-116 25 October 1948

To: Comdts., All Naval Districts, Potomac and Severn River Naval Commands, Chief, Naval Air Training, and Fleet and Force Commanders.

Attn: District and Staff Medical Officers.

Subj: Training of Hospital Corps Enlisted X-Ray Technicians in Photodosimetry.

In this letter, the addressees are requested, (1), insofar as practical, to assign to temporary additional duty in each administrative command, one or more Hospital Corps x-ray technicians, previously trained and designated a specialist in photodosimetry, for the purpose of instructing as many x-ray technicians on board in activities of the command as circumstances will permit, and (2) to make an appropriate entry in the service record of each man who qualifies in photodosimetry technic with a list of names of such men to BuMed.

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